

BEST AVAILABLE COPY

PATENT SPECIFICATION

NO DRAWINGS

834028



Date of Application and filing Complete Specification: Aug. 10, 1956.

No. 24609/56.

Application made in United States of America on Aug. 22, 1955.

Complete Specification Published: May 4, 1960.

Index at acceptance:—Class 2(3), C1F2(C4: C6: C7: D3), C2A(3: 14), C2B4(A4: C: D: F: G1: G4: G8), C2B(7: 9: 18: 20), C2R17, C3A8, C3A10A(4G: 5K), C3A12(A4A: A4C: B3: C1), C3A14A(3D: 5: 8D).

International Classification:—C07d.

COMPLETE SPECIFICATION

3-Indolyl Aminohydrocarbyl Ketones

We, THE UPJOHN COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

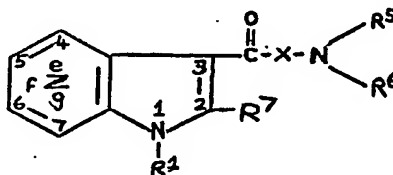
The present invention relates to a novel process for the preparation of 3-indolyl aminohydrocarbyl ketones and more especially to the preparation of 1-hydro-3-indolyl aminohydrocarbyl ketone free bases and addition compounds thereof such as acid addition salts, amine oxides, amine oxide-ammonium salts, and to novel 1-dehydro-3-indolyl aminohydrocarbyl ketone free bases and addition compounds thereof.

The term "hydrocarbyl" as used herein includes any hydrocarbon radical which connects the amino fragment of the 3-indolyl aminohydrocarbyl ketone to the carbonyl group which is attached to the indole nucleus at position 3. The term "dehydro" is used to denote the absence of hydrogen in the 1-position of the indole nucleus in contrast to a 1-hydroindole.

The 3-indolyl aminohydrocarbyl ketones of the present invention are produced by reacting a 3-acylindole containing a hydrogen atom alpha to the carbonyl group with an aldehyde in the presence of ammonia or a primary or a secondary amine. The acyl substituent of the starting indole is from an organic carboxylic acid. The use of ammonia results in the preparation of a primary amino-ketone and the use of a primary or secondary

amine results in the production of a secondary or tertiary amino-ketone respectively.

The 3-indolyl aminohydrocarbyl ketones produced by the novel process of the present invention can be represented by the formula: 45



wherein R⁵ and R⁶ taken individually represent hydrogen, aryl, aralkyl, or alkyl and together contain not more than fifteen carbon atoms, or R⁵ and R⁶ taken together with —N< can also represent a heterocyclic amino radical, such as morpholinyl, piperidyl, pyrrolidyl, thiamorpholinyl, hexamethylene-imino, decahydroisoquinolyl or hexahydro-isoquinolyl (both cis and trans). X is a vicinal divalent saturated hydrocarbyl radical containing not more than fifteen carbon atoms. A vicinal divalent saturated hydrocarbyl radical is a saturated hydrocarbyl radical having the valences separated by two carbon atoms, i.e., is an unsubstituted or hydrocarbon-substituted ethylene radical. Thus in the compounds of the invention the carbonyl group and the amino nitrogen atom are separated by two carbon atoms. R¹ represents hydrogen; an alkyl radical containing up to twenty carbon atoms such as methyl, ethyl, propyl, hexyl, decyl and hexadecyl; an aryl radical containing up to fifteen carbon atoms such as phenyl, naphthyl, biphenyl; a haloaryl radical such as para-chlorophenyl; 50 55 60 65 70

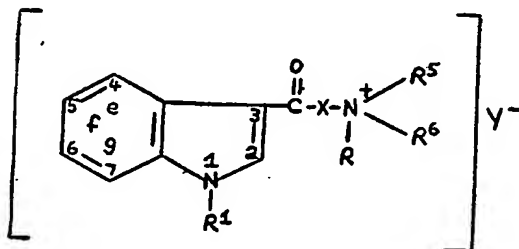
[Price 3s. 6d.]

- an alkoxyaryl radical such as 2-ethoxynaphthyl; or an aralkyl radical containing up to fifteen carbon atoms such as benzyl, phenethyl, phenylbutyl; a halobenzyl radical, such as para-chlorobenzyl; an alkylbenzyl radical, such as para-methylbenzyl; an alkoxybenzyl radical, such as para-methoxybenzyl. R' is hydrogen, lower alkyl of from 1 to 8 carbon atoms inclusive, or an aryl or aralkyl radical and the benzene ring Z may contain additional substituents as hereinafter specified.
- The 4-, 5-, 6-, and 1-positions of the benzene ring can include the following substituents as hydroxy; halogen, e.g., chlorine and bromine; a cyano radical; a carboxy radical; a lower-carbalkoxy radical containing up to eight carbon atoms, e.g., carbomethoxy and carbobutoxy; a dialkyl-amino radical, e.g., dimethylamino and diethylamino; a benzyloxy radical, e.g., benzyl-oxy; and benzhydryloxy, a chloro-, alkyl- or alkoxy-substituted benzyloxy and a lower-alkoxy radical containing up to nine carbon atoms, e.g., methoxy and octoxy; an acyloxy radical wherein the acyl substituent is from an organic carboxylic acid containing from one to eight carbon atoms, e.g., acetoxy, propionoxy and capryloxy; a lower-alkyl radical containing up to nine carbon atoms, e.g. methyl, ethyl, propyl and octyl; an unsubstituted aralkyl radical, e.g., benzyl and phenethyl; an unsubstituted aryl radical, e.g., phenyl and naphthyl; an aryloxy radical, e.g., phenoxy and naphthoxy; and a fused arylene radical, e.g., phenylene and naphthylene. A fused arylene radical encompasses a divalent arylene radical which is fused at positions e, f, or g of the benzene ring of the indole nucleus.
- The 4-, 5-, 6-, and 7-position substituents can be alike or different but it is understood that hydrogen is located in the positions not occupied by substituents.
- The various 2-, 4-, 5-, 6-, and 7-substituted indoles which can be employed as starting compounds in the present invention can be prepared by utilizing the procedures outlined in copending application No. 8887/56 (Serial No. 797,258).
- The starting 3-acylindoles can be prepared by the processes outlined in "Heterocyclic Compounds," Elderfield, Volume 3, Page 44, 1952—John Wiley and Sons, Inc. For example, 3-indolyl methyl ketone can be prepared by reacting acetyl chloride with 3-indolylmagnesium iodide; 3-(2-methylindolyl) methyl ketone can be prepared by reacting 2-methylindole with acetic anhydride and sodium acetate; 3-(2-methylindolyl) benzyl ketone can be prepared by reacting 2-methylindole with benzyl cyanide.
- 1-Dehydro-3-acylindoles can be prepared by utilizing the procedure of Baker, J. Chem. Soc. 1940, 458—60. For example, 1-alkyl-3-acylindoles can be prepared by reacting a 3-acylindole with an alkyl halide in the presence of an alkali-metal alkoxide. Similarly, 1-aryl and 1-aralkyl-3-acylindoles can be produced by substituting an aryl or aralkyl halide for the alkyl halide in the Baker process.
- In carrying out the process of the present invention a 3-acylindole is mixed with an aldehyde and a primary or secondary amine, or with ammonia, in the presence of an inert solvent. The reaction is generally carried out under acid conditions, i.e., a pH of less than seven. Various aldehydes can be employed, e.g., aliphatic aldehydes such as aqueous formaldehyde, para-formaldehyde, acetaldehyde, *n*-butyraldehyde and *n*-valeraldehyde; aromatic aldehydes, e.g., benzaldehyde, phenylacetaldehyde and para-methylbenzaldehyde. Inert solvents can include methanol, ethanol, and isoamyl alcohol although when aqueous formaldehyde is employed no solvent is necessary. Various primary and secondary amines can be employed in the reaction such as the primary or secondary alkyl, cycloalkyl, aralkyl, and aryl amines, as well as alkylaralkyl amines and heterocyclic amines. Representative amines include methylamine, dimethylamine, ethylamine, diethylamine, diisopropylamine, benzylamine, dibenzylamine, aniline, methyl-aniline, allylamine, piperidine, thiomorpholine, pyrrolidine and morpholine.
- The acid conditions generally necessary for completion of the reaction can be brought about by adding the amine as an acid addition salt such as the hydrochloride, sulphate, or hydrobromide. The acid conditions can also be brought about by the addition of an acid such as acetic, hydrochloric, phosphoric, sulphuric, or hydrobromic to the reaction mixture.
- The reaction is carried out at a temperature between about fifty and about 100 degrees centigrade, advantageously at a temperature between about 65 and about 85 degrees centigrade. The reaction is generally completed after a period of about 24 hours.
- The thus-produced 3-indolyl aminohydrocarbyl ketone can be recovered in a conventional manner from the reaction mixture. For example, the 3-indolyl aminohydrocarbyl ketone acid addition salt precipitate can be recovered by filtration after cooling the reaction mixture. The free base can be recovered by dissolving the acid addition salt in water, extracting with ether, and adding excess alkali-metal hydroxide to the aqueous mixture. The resulting mixture can be extracted with ether and the ether extracts washed with a saturated salt solution. The washed product can thereupon be dried and the resulting dried mixture evaporated and triturated to produce the free base.
- In some instances the acid addition salt is extremely soluble and will not readily

precipitate upon cooling from the reaction mixture. In such cases, however, the acid addition salt can be recovered by initially isolating the free base which can be isolated by extracting the reaction mixture with ether, adding a cold solution of an alkali-metal hydroxide, extracting with chloroform, drying the chloroform extract over sodium sulphate, and evaporating the chloroform. The acid addition salt can then be isolated by adding the desired acid to a chloroform solution of the free base.

The 3-indolyl aminohydrocarbyl ketone N-oxide can be prepared by reacting the tertiary amine free base with an oxidizing agent such as hydrogen peroxide or peracetic acid, and 3-indolyl aminohydrocarbyl ketone N-oxide acid addition salts can be prepared by reacting 3-indolyl aminohydrocarbyl ketone N-oxide dissolved, e.g., in ethyl alcohol-ethyl acetate, with an acid such as hydrochloric, hydrobromic, sulphuric, acetic, tartaric or citric.

The 3-indolyl aminohydrocarbyl ketones can also be converted to novel and useful quaternary ammonium salts by reacting the tertiary amine free base in an inert solvent with a suitable quaternary ammonium salt-forming compound such as methyl iodide, ethyl bromide, octyl bromide, benzyl chloride, dimethyl sulphate, and methyl para-toluenesulphonate. The 3-indolyl aminohydrocarbyl ketone quaternary ammonium salts can be represented by the following general formula:



wherein X and R¹ have the same values represented above, and R⁵ and R⁶ taken individually represent aryl, aralkyl, or alkyl and together contain not more than fifteen carbon atoms, or when taken together with —N< represent a heterocyclic amino radical such as morpholinyl, piperidyl, pyrrolidyl, thiamorpholinyl, hexamethyleneimino, decahydroisoquinolyl or hexahydroisoquinolyl (both cis and trans); R⁵ and R⁶ together contain not more than fifteen carbon atoms; R represents aralkyl and alkyl and contains not more than eight carbon atoms and Y represents an anion, such as a halogen anion, e.g., a chloride, iodide, or bromide anion; a sulphate anion, e.g., that derived from diamethyl sulphate; or a para-toluenesulphonate anion, e.g., that derived from methyl para-

toluenesulphonate. The 2-, 4-, 5-, 6-, and 7-positions can be similarly substituted at noted above.

The 3-indolyl aminohydrocarbyl ketones produced by the novel process of the present invention have hypotensive and diuretic activity. In addition, the 3-indolyl aminohydrocarbyl ketones can be converted by lithium aluminium hydride to pharmacologically active 3-(aminohydrocarbyl)-indoles, e.g., 3-(3¹-dimethylaminopropyl)-indole can be produced by reducing 2¹-dimethylaminoethyl 3-indolyl ketone with lithium aluminium hydride in tetrahydrofuran. The 3-(aminohydrocarbyl)-indoles also have hypotensive activity.

Furthermore, the 3-indolyl aminohydrocarbyl ketones can be reacted with fluosilicic acid to form the fluosilicate salts which in dilute aqueous solutions are effective moth-proofing agents as more fully disclosed in U.S. Patents 2,075,359 and 1,915,334.

The novel 3-indolyl aminohydrocarbyl ketone quaternary ammonium salts can be employed as intermediates for the preparation of auxins (plant growth substances), e.g., 2-dimethylaminoethyl 3-indolyl ketone methiodide can be reacted with sodium cyanide to produce 3-(γ-cyanopropionyl)-indole, the later subjected to alkaline hydrolysis to produce the keto acid, and the latter reduced utilizing the procedure of Huang-Minlon [J. Am. Chem. Soc. 68, 2487 (1946)] to produce 3-indolebutyric acid ("Agricultural Chemistry," Frear, Vol. 1, Page 427, 1952, D. Van Nostrand Co.). The Huang-Minlon technique involves refluxing the ketone with diethylene glycol, hydrazine hydrate, and sodium hydroxide, distilling off the water and hydrazine hydrate to raise the temperature to 180 to 200 degrees centigrade and refluxing again for three to four hours. Alternatively, 3-indolebutyric acid can also be produced by subjecting the keto acid to hydrogenation utilizing five percent palladium on carbon in alcohol.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1

2¹-dibenzylaminoethyl 3-indolyl ketone
A. 2¹-dibenzylaminoethyl 3-indolyl ketone hydrochloride

A mixture of 4.35 grams of 3-indolyl methyl ketone (Saxton, J. Chem. Soc. 1952, 3592), 6.4 grams of dibenzylamine hydrochloride, 1.23 grams of paraformaldehyde and 41 milliliters of absolute ethanol was refluxed for 24 hours. The solution was cooled to about 25 degrees centigrade and crystallization thereupon occurred. The cooled mixture was filtered and the precipitate was washed with methanol and ether to yield 2-dibenzylaminoethyl 3-indolyl ketone hydro-

chloride which melted at 189 to 189.5 degrees centigrade.

Anal.: Calcd. for $C_{25}H_{25}N_2OCl$: Cl, 8.76

Found: Cl, 8.85.

5 B. 2-dibenzylaminoethyl-3-indolyl ketone
free base

The hydrochloride from Part A was dissolved in water and extracted with ether. Excess potassium hydroxide was added to the aqueous mixture and the resulting mixture

was extracted with ether. The resulting ether extract was washed with a saturated salt solution, dried over sodium sulphate, and evaporated to produce an oil. The resulting oil was triturated with ether-petroleum ether and recrystallized from benzen-petroleum ether to produce 2¹-dibenzylaminoethyl 3-indolyl ketone free base which melted between 130.5 to 132 degrees centigrade.

20 Anal.: Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.97, N, 7.61
Found: C, 81.38; H, 6.35; N, 7.78.

EXAMPLE 2

2¹-dimethylaminoethyl 3-(5-benzoyloxyindolyl) ketone

25 A. 3-(5-benzoyloxyindolyl) methyl ketone

5-benzoyloxyindole (11.15 grams; 0.05 mole) dissolved in 100 milliliters of ether and 100 milliliters of benzene was added during five minutes to a Grignard reagent prepared from magnesium (2.68 grams; 0.11 mole) and methyl iodide (17 grams; 0.12 mole). The mixture was refluxed for 75 minutes. It was then cooled in ice and 8.65 grams (0.11 mole) of acetyl chloride in 25 milliliters of ether was added dropwise. The resulting mixture was stirred for three hours at about 25 degrees centigrade. The mixture was then cooled in ice and acidified with a solution of

fifteen milliliters of acetic acid in fifty milliliters of water. After stirring for fifteen minutes the precipitate was filtered, washed with water and ether and suspended in fifty milliliters of ethanol. A solution of three grams of potassium hydroxide in ten milliliters of water was added and the resulting solution was evaporated to about half its volume to yield 5.95 grams of 3-(5-benzoyloxyindolyl) methyl ketone which was recrystallized from ethanol and melted at 188 to 190 degrees centigrade. Infrared and ultraviolet was in accord with the proposed structure. The filtrate was evaporated further to yield an additional quantity of 3-(5-benzoyloxyindolyl)methyl ketone.

55 Anal.: Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28
Found: C, 77.36; H, 5.43; N, 5.39.

B. 2¹-dimethylaminoethyl 3-(5-benzoyloxyindolyl) ketone hydrochloride

60 A mixture of 2.65 grams of 3-(5-benzoyloxyindolyl)methyl ketone (0.01 mole), 0.98 gram of dimethylamine hydrochloride (0.012 mole), 0.6 gram of paraformaldehyde and 25 milliliters of absolute ethanol was refluxed for 26 hours. Crystals appeared after a few hours of refluxing. The mixture was allowed to stand for twelve hours and was then cooled

in ice, filtered, and washed with cold methanol and ether to yield 2.48 grams of 2¹-dimethylaminoethyl 3-(5-benzoyloxyindolyl) ketone hydrochloride. The hydrochloride was recrystallized twice by dissolving in 75 milliliters of absolute ethanol and evaporating to forty milliliters. The recrystallized hydrochloride melted between 199.5 degrees to 200.5 degrees centigrade.

Anal.: Calcd for $C_{20}H_{23}N_2O_2 \cdot Cl$: C, 66.93; H, 6.46; N, 7.81; Cl, 9.88
Found: C, 67.36; H, 6.86; N, 8.05; Cl, 9.82.

C. 2¹-dimethylaminoethyl 3-(5-benzoyloxyindolyl) ketone free base

80 The hydrochloride from Part B was reacted with potassium hydroxide in the same manner as shown in Example 1, Part B, to produce 2¹-dimethylaminoethyl 3-(5-benzoyloxyindolyl) ketone free base.

EXAMPLE 3

2¹-dimethylaminoethyl 3-indolyl ketone

A. 2¹-dimethylaminoethyl 3-indolyl ketone free base

90 A mixture of 3-indolyl methyl ketone (15.9 grams; 0.01 mole), dimethylamine hydrochloride (8.15 grams; 0.1 mole) paraformaldehyde (4.5 grams; 0.15 mole) and 150 milliliters of absolute ethanol was refluxed for 24 hours. The clear brown solution was allowed to stand at 25 degrees centigrade

for 24 hours and was then evaporated under vacuum to a viscous oil. Water (200 milliliters) was added and the mixture was filtered. The aqueous filtrate was extracted twice with ether. The clear aqueous solution was then cooled in ice and made alkaline with a cold solution of potassium hydroxide (10 grams) in 25 milliliters of water. The resulting oil was extracted thrice with chloroform and the chloroform extracts were washed twice with a saturated salt solution, and dried over sodium sulphate. The chloroform was removed by evaporation to produce 13.1 grams of 2¹-dimethylaminoethyl 3-indolyl ketone free base. The compound melted at 116 to 118.5 degrees centigrade and had the following analysis:

Anal.: Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.96
Found: C, 72.37; H, 7.28; N, 12.72.

B. 2¹-dimethylaminoethyl 3-indolyl ketone hydrochloride

- 5 To a chloroform solution of 2¹-dimethylaminoethyl 3-indolyl ketone free base was added gaseous hydrogen chloride and the

resulting precipitate, 2¹-dimethylaminoethyl 3-indolyl ketone hydrochloride, melted at 179 to 180 degrees centigrade and had the following analysis:

Anal.: Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09
Found: C, 61.36; H, 6.93; Cl, 13.97; N, 10.69.

EXAMPLE 4

- 15 2¹-dimethylaminoethyl 3-indolyl ketone methiodide

Methyl iodide (1.42 grams; 0.1 mole) was added to a solution of 1.08 grams of 2¹-dimethylaminoethyl 3-indolyl ketone free base, prepared as disclosed in Example 3, Part A, in six milliliters of methanol cooled in ice.

The mixture was allowed to stand in the cold for four hours. The mixture was filtered and the precipitate washed with cold methanol to produce 1.53 grams of 2¹-dimethylaminoethyl 3-indolyl ketone methiodide which melted at 205.5 to 207.5 degrees centigrade (87 percent yield).

Anal.: Calcd. for $C_{14}H_{19}N_2IO$: C, 46.94; H, 5.35; N, 7.82; I, 35.43
Found: C, 47.03; H, 5.50; N, 7.58; I, 35.39.

EXAMPLE 5

- 2¹-dibenzylaminoethyl 3-indolyl ketone ethiodide

35 In the same manner as shown in Example 4, 2¹-dibenzylaminoethyl 3-indolyl ketone ethiodide was prepared by reacting 2¹-dibenzylaminoethyl 3-indolyl ketone free base (Example 1, Part B) with ethyl iodide.

EXAMPLE 6

- 40 2¹-dimethylaminoethyl 3-(5-benzzyloxyindolyl) ketone benzyl chloride

In the same manner as shown in Example 4, 2¹-dimethylaminoethyl 3-(5-benzzyloxyindolyl) ketone benzyl chloride was prepared by reacting 2¹-dimethylaminoethyl 3-(5-benzzyloxyindolyl) ketone free base (Example 2, Part C) with benzyl chloride.

EXAMPLE 7

- 50 1¹-methyl-2¹-diethylaminoethyl 3-indolyl ketone methiodide

In the same manner as shown in Example 2, Parts A, B, and C, 1¹-methyl-2¹-diethylaminoethyl 3-indolyl ketone free base was prepared by utilizing indole, propionyl chloride, and diethylamine hydrochloride, in lieu of 5-benzzyloxyindole, acetyl chloride, and dimethylamine hydrochloride. The resulting compound was reacted with methyl iodide in the same manner as shown in Example 4 to produce 1¹-methyl-2¹-diethylaminoethyl 3-indolyl ketone methiodide.

EXAMPLE 8

- 65 1¹-ethyl-2¹-diethylaminoethyl 3-indolyl ketone methobromide

In the same manner as shown in Example 2, Parts A, B, and C, 1¹-ethyl-2¹-diethylaminoethyl 3-indolyl ketone free base was prepared by utilizing indole, *n*-butyryl chloride, and diethylamine hydrochloride in lieu of 5-benzzyloxyindole, acetyl chloride, and dimethylamine hydrochloride. The resulting compound was reacted with methyl bromide in the same manner as shown in Example 4

to produce 1¹-ethyl-2¹-diethylaminoethyl 3-indolyl ketone methobromide.

EXAMPLE 9

- 2¹-dimethylaminoethyl 3-indolyl ketone N-oxide

A mixture of hydrogen peroxide and 2¹-dimethylaminoethyl 3-indolyl ketone free base, Example 3, Part A, in methyl alcohol was shaken for twenty hours. The mixture was allowed to stand for four days whereupon an aqueous slurry of platinum-on-charcoal was added to decompose the excess hydrogen peroxide. When oxygen evolution had ceased the mixture was shaken for about five hours, filtered, and the filtrate evaporated to dryness. The crystalline residue was recrystallized from ethyl acetate to yield 2¹-dimethylaminoethyl 3-indolyl ketone N-oxide.

EXAMPLE 10

- 2¹-dimethylaminoethyl 3-indolyl ketone N-oxide hydrochloride

2¹-dimethylaminoethyl 3-indolyl ketone N-oxide hydrochloride was produced by dissolving 2¹-dimethylaminoethyl 3-indolyl ketone N-oxide, Example 9, in ethyl alcohol-ethyl acetate and passing gaseous hydrogen chloride into the mixture.

EXAMPLE 11

- 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone

A. 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone hydrochloride

A mixture of 13.6 grams of 1-methyl-3-acetylindole [C.A. 49, 1006^a (1955)], 6.4 grams of dimethylamine hydrochloride, 3.54 grams of paraformaldehyde, and 120 milliliters of ethanol was refluxed for 24 hours. The solution was evaporated under vacuum and the resulting crude solid was recrystallized twice from methanol to yield 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone hydrochloride which melted at 185 to 186 degrees centigrade.

Anal. Calcd. for $C_{14}H_{18}N_2ClO$: C, 63.03; H, 7.35; N, 10.50; Cl, 13.29
 Found: C, 62.81; H, 6.93; N, 9.96; Cl, 13.33.

B. 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone free base

5 In the same manner as shown in Example 1, Part B, 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone free base was prepared by reacting 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone hydrochloride with potassium hydroxide.

10 C. 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone methiodide

In the same manner as shown in Example 4, 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone methiodide was prepared by reacting 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone free base with methyl iodide.

D. 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone N-oxide

20 In the same manner as shown in Example 10, 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone N-oxide was prepared by reacting 2¹-dimethylaminoethyl 3-(1-methyl-indolyl) ketone free base with hydrogen peroxide.

E. 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone N-oxide hydrochloride

25 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone N-oxide hydrochloride was prepared by dissolving 2¹-dimethylaminoethyl 3-(1-methylindolyl) ketone N-oxide in ethyl alcohol-ethyl acetate and passing gaseous hydrogen chloride into the mixture.

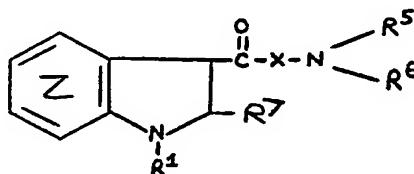
30 Additional 3-indolyl aminohydrocarbyl ketones which can be produced by the present invention include the following: 2¹-methylbenzylaminoethyl 3-(4-methylindolyl) ketone free base, 1¹-phenyl-2¹-diethylaminoethyl 3-(1-ethyl-4-chloroindolyl) ketone ethiodide, 2¹-ethyl-2¹-methylbenzylaminoethyl 3-(6-methoxyindole) ketone free base, 2¹-morpholinoethyl 3-(4-benzyloxyindolyl) ketone benzyl chloride, 2¹-(α -naphthyl)-2¹-dimethylaminoethyl 3-(5-benzhydryloxyindolyl) ketone free base, 2¹-methyl-2¹-morpholinoethyl 3-(2-ethyl-5-ethoxyindolyl) ketone ethobromide, 2¹-phenylethyl-2¹-methylbenzylaminoethyl 3-(5-benzyloxyindolyl) ketone dimethyl sulphate, 2¹-dimethylaminoethyl 3-(1-benzyl-5-acetoxyindolyl) ketone methyl para-toluenesulphonate, 2¹-benzyl-2¹-methylbenzylaminoethyl 3-(6-methoxyindolyl) ketone free base, 2¹-dipropylaminoethyl 3-(5,6-diethoxyindolyl) ketone free base, 2¹-dibenzylaminoethyl 3-indolyl ketone N-oxide, 2¹-pyrrolidinoethyl 3-(4-dimethylaminoindolyl) ketone free base, 2¹-ethylbenzylaminoethyl 3-(1-propyl-5-carbethoxyindolyl) ketone free base, 2¹-benzylaminoethyl 3-(1-phenyl-4-carboxyindolyl) ketone free base, 2¹-anilinoethyl 3-(2,5-diphenylindolyl) ketone free base, 2¹-piper-

idinoethyl 3-(2,6-dibenzyloxyindolyl) ketone 6¹
 hydrochloride, 1¹-methyl-2¹-ethylphenylaminoethyl 3-(5-phenoxyindolyl) ketone
 N-oxide sulphate, 2¹-dibutylaminoethyl 3-[1-benz(g)indolyl] ketone free base, 7¹
 and 1¹-ethyl-2¹-diethylaminoethyl 3-(5-para-chlorobenzyloxyindolyl) ketone N-oxide.

WHAT WE CLAIM IS:—

1. A process for the preparation of 3-indolyl aminohydrocarbyl ketones as hereinbefore specified, which comprises reacting a 3-acylindole containing a hydrogen atom alpha to the carbonyl group, an aldehyde and ammonia, a primary amine, or a secondary amine at a pH of less than seven. 80

2. A process as claimed in claim 1 wherein the 3-indolyl amino-hydrocarbyl ketone so produced has the general formula:



wherein X is a vicinyl divalent saturated hydrocarbyl radical containing not more than fifteen carbon atoms, R¹ is hydrogen, alkyl, aryl or aralkyl, R⁵ and R⁶ are hydrogen aryl, aralkyl or alkyl, or wherein R⁵ and R⁶ together with -N< form a heterocyclic amino radical, R⁷ is hydrogen, lower alkyl of from 1 to 8 carbon atoms inclusive or an aryl or aralkyl radical and the benzene ring Z may contain additional substituents as hereinbefore specified. 95

3. A process as claimed in claim 1 or 2 wherein 3-indolyl methyl ketone is reacted with paraformaldehyde and dimethylamine at a pH of less than seven and the product is 2¹-dimethylaminoethyl-3-indolyl ketone. 100

4. A process as claimed in claim 1 or 2 wherein 3-(5-benzyloxyindolyl) methyl ketone is reacted with para-formaldehyde and dimethylamine at a pH of less than seven and the product is 2¹-dimethylaminoethyl-3-(5-benzyloxyindolyl) ketone. 105

5. A process as claimed in claim 1 or 2 wherein 3-indolyl methyl ketone is reacted with paraformaldehyde and dibenzylamine at a pH of less than seven, and the product is 2¹-dibenzylaminoethyl 3-indolyl ketone. 110

6. A process for the preparation of 2¹-dimethylaminoethyl 3-(5-benzyloxyindolyl) ketone hydrochloride which comprises reacting 5-benzyloxyindole with a Grignard reagent, reacting the thus-produced 5-benzyloxyindolemagnesium halide with acetyl-

chloride to produce 3-(5-benzoyloxyindolyl) methyl ketone, and reacting 3-(5-benzoyloxyindolyl) methyl ketone, dimethylamine hydrochloride and paraformaldehyde at a pH of less than seven.

7. A process for the preparation of quaternary ammonium salts of 3-indolyl aminohydrocarbyl ketones which comprises reacting a 3-acylindole containing a hydrogen atom alpha to the carbonyl group, an aldehyde, and a secondary amine acid addition salt to produce a 3-indolyl aminohydrocarbyl ketone acid addition salt, deacidifying the acid addition salt to produce a 3-indolyl aminohydrocarbyl ketone free base, and reacting the 3-indolyl aminohydrocarbyl ketone free base with a quaternary ammonium salt-forming compound.

8. A process as claimed in claim 1 or 2 wherein an aliphatic aldehyde and a diaralkylamine are employed.

9. A process as claimed in claim 1 or 2 wherein an aliphatic aldehyde and a dialkylamine are employed.

10. A process as claimed in claim 1 or 2 wherein an aliphatic aldehyde and an alkylaralkylamine are employed.

11. A process as claimed in claim 1 or 2 wherein an aliphatic aldehyde and an alkylamine are employed.

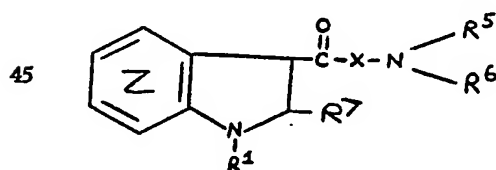
12. A process as claimed in claim 1 or 2 wherein an aromatic aldehyde and a diaralkylamine are employed.

13. A process as claimed in claim 1 or 2 wherein an aromatic aldehyde and an alkylaralkylamine are employed.

14. A process as claimed in claim 1 or 2 wherein an aromatic aldehyde and a dialkylamine are employed.

15. A process as claimed in claim 1 or 2 wherein an aromatic aldehyde and an alkylamine are employed.

16. A 1-dehydro-3-indolyl aminohydrocarbyl ketone having the general formula:

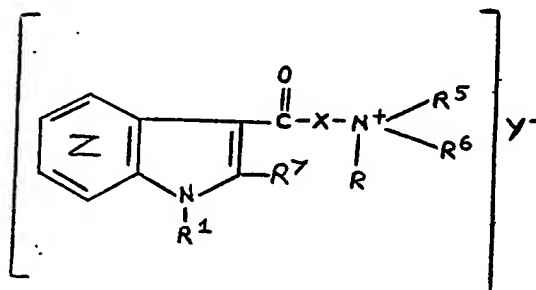


wherein X is a vicinyl divalent saturated hydrocarbyl radical containing not more than fifteen carbon atoms, R¹ represents an alkyl radical containing not more than twenty carbon atoms, an aryl radical containing up to fifteen carbon atoms or an aralkyl radical containing up to fifteen carbon atoms, R⁵ and R⁶ are hydrogen, aryl, aralkyl or alkyl and together contain not more than fifteen carbon atoms, or R⁵ and R⁶ together with —N< form a heterocyclic amino

radical, R⁷ is hydrogen, lower alkyl of from 1 to 8 carbon atoms inclusive or an aryl or aralkyl radical and the benzene ring Z may contain additional substituents as hereinbefore specified.

17. A 1-dehydro-3-indolyl aminohydrocarbyl ketone free base, a 1-dehydro-3-indolyl aminohydrocarbyl ketone acid addition salt, a 1-dehydro-3-indolyl aminohydrocarbyl ketone quaternary ammonium salt, a 1-dehydro-3-indolyl aminohydrocarbyl ketone N-oxide and a 1-dehydro-3-indolyl aminohydrocarbyl ketone N-oxide acid addition salt.

18. Quaternary ammonium compounds having the general formula:



wherein X is a vicinyl divalent saturated hydrocarbyl radical containing not more than fifteen carbon atoms, R¹ represents hydrogen, an alkyl radical containing not more than twenty carbon atoms, an aryl radical containing up to fifteen carbon atoms, or an aralkyl radical containing up to fifteen carbon atoms, R⁵ and R⁶ taken individually are aryl, aralkyl, or alkyl radicals, and together contain not more than fifteen carbon atoms or R⁵ and R⁶ taken together with —N< form a heterocyclic amino radical, R is an aralkyl or alkyl radical containing not more than eight carbon atoms, Y is an anion, R⁷ is hydrogen, lower alkyl of from 1 to 8 carbon atoms inclusive or an aryl or aralkyl radical and the benzene ring Z may contain additional substituents as hereinbefore specified.

19. 2¹ - Dimethylaminoethyl 3 - indolyl ketone methiodide.

20. 2¹ - Dibenzylaminoethyl 3 - indolyl ketone ethiodide.

21. 2¹-Dimethylaminoethyl 3 - (5 - benzoyloxyindolyl) ketone benzyl chloride.

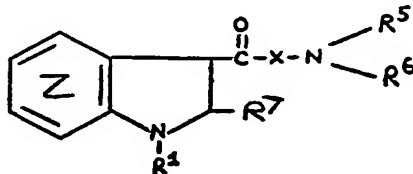
22. 1¹ - Methyl - 2¹ - diethylaminoethyl 3 - indolyl ketone methiodide.

23. 1¹ - Ethyl - 2¹ - diethylaminoethyl 3 - indolyl ketone methobromide.

24. A process for the preparation of 3-indolyl aminohydrocarbyl ketones substantially as herein-described with reference to the Examples.

25. A 3-indolyl aminohydrocarbyl ketone

having the general formula:



5 wherein X is a vicinal divalent saturated hydrocarbyl radical containing not more than fifteen carbon atoms, R¹ represents hydrogen, an alkyl radical containing not more than twenty carbon atoms, an aryl radical containing up to fifteen carbon atoms, an

10 aralkyl radical containing up to fifteen carbon atoms, and is an aryl, aralkyl or alkyl radical, R⁵ and R⁶ are hydrogen, aryl, aralkyl or alkyl and together contain not more than fifteen carbon atoms, or R⁵ and R⁶ together with —N< form a heterocyclic amino radical, R⁷ is hydrogen, lower alkyl of from 1 to 8 15 carbon atoms inclusive or an aryl or aralkyl radical, and the benzene ring Z may contain additional substituents specified, when prepared by a process as claimed in any of 20 claims 1 to 5 or 8 to 15 or 24.

For the Applicants:—
GILL, JENNINGS & EVERY,
Chartered Patent Agents,
51/52, Chancery Lane,
London, W.C.2.